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09/485,879	06/22/2000	MICHAEL GIESING	790076.401	6896

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SEED INTELLECTUAL PROPERTY LAW GROUP
701 FIFTH AVENUE
SUITE 6300
SEATTLE, WA 98104-7092

EXAMINER

GOLDBERG, JEANINE ANNE

ART UNIT PAPER NUMBER

1634

DATE MAILED: 06/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/485,879	Applicant(s) GIESING ET AL.	
	Examiner Jeanine A Goldberg	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 March 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 21,22,24-39 and 41-60 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 21,22,24-39 and 41-60 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. This action is in response to the papers filed March 4, 2003. Currently, claims 21-22, 24-39, 41-60 are pending. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.
 2. It is noted that the Appendix of Currently Pending claims does not appear to contain Claim 31. Claim 31 has not been cancelled.
 3. Any objections and rejections not reiterated below are hereby withdrawn in view of applicant's response and the amendments to the claims. The action contains new grounds of rejection necessitated by amendment.
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Priority

4. This application is a 371 of PCT/EP/98/05360, filed August 24, 1998. This application also claims priority to foreign document 197 36 691.0, filed August 22, 1997, however, a translation of this document has not been provided.

Applicant's request clarification from the Examiner regarding the reference to the priority document in the first paragraph. The examiner has not required or even requested a translation. The examiner has merely indicated that the translation has not been provided.

New Grounds of Rejection Necessitated by Amendment

New Matter

5. Claims 21-22, 24-37, 41-60 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the amended claims, reference to "wherein the first fraction has not been subjected to a method for isolating cancer cell" are included. The amendment does not specifically point to support in the specification for the amendments. However, the specification does not describe or discuss "wherein the first fraction has not been subjected to a method for isolating cancer cell" and "detecting in at least one non-cancer cell from the subject an absence or presence of the at least one second nucleic acid that is detected in step (c)." Instead the specification describes a "method for the

characterization of disseminated and micro metastasized cancer cells on the basis of DNA and/or RNA, wherein cells obtained from body fluid from an individual are investigated for at least one cancer- specific gene on the basis of mRNA; and/or cancer cells removed from body fluid from an individual are investigated for at least one cancer-specific gene on the basis of DNA and/or mRNA, and the same investigation is carried out with non-cancer cells from the same individual for comparison.” Page 4 of the Specification. The specification also exemplifies a “reference Example 1” which teaches the isolation of fraction A which was not enriched for cancer cells (page 31). The specification then exemplifies a separate example which isolates tumor cells in fraction C. The specification does not appear to provide a single example teaching isolating cancer cells in one fraction and NOT isolating cancer cells in a separate fraction. The single passage in the specification which appears to contemplate a two assay method is silent with respect NOT isolating from a first fraction. Therefore, this appears to be new matter. The concept of “wherein the first fraction has not been subjected to a method for isolating cancer cell” does not appear to be part of the originally filed invention. Therefore, “wherein the first fraction has not been subjected to a method for isolating cancer cell” constitutes new matter. Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 21-22, 24-28, 32, 36-37, 41-45, 49-51, 54-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jung et al. (Eur. J. Clinical Chemistry and Clinical Biochemistry. Vol. 35, No. 1, pages 3-10 January 1, 1997) and Rimm et al (US Pat. 6,197,523, March 2001) or Ts'o et al (US Pat 5,962,237, October 1999) in view of Hoon et al (US Pat 6,057,105, May 2, 2000).

This rejection is based upon the interpretation of the claims to encompass detection of a nucleic acid in both an enriched sample and in a sample which has not been enriched for cancer cells.

Jung et al. (herein referred to as Jung) teaches the quality management and influential factors for the detection of single metastatic cancer cells by reverse transcriptase polymerase chain reaction. Jung teaches that the amplification of tissue-

specific gene expression, by RT-PCR readily detects single tumor cell sin different tissues. Jung teaches the method is sensitive and specific for detection of mircrometataasis which holds great promise for earlier staging of cancer patients (abstract). Jung provides a table of genes which have been detected using RT-PCR. Jung teaches numerous reasons why it is advantageous to perform a high-sensitivity RT-PCR on peripheral blood sample, including ease for patient, ease for lab in assaying and sensitivity and specificity (page 5, col. 1)(limitations of Claim 41b)

Rimm et al (herein referred to as Rimm) teaches a method for the detection, identification, enumeration and confirmation of circulating cancer and or hematologic progenitor cells in whole blood. Rim teaches the analysis involved epitopic examination of the blood sample, while the blood sample is disposed in a centrifuged blood sampling tube such that the epitopic analysis of the presence or absence of cancer cells relies on the detection of epitopes which are known to be present only on cancer cells (abstract). Rimm teaches that epithelial-specific antigens such as CEA may be used (limitations of Claim 23-26)(col. 4, lines . 49-52). Rimm teaches that "additional scans depending on what additional cellular information is being sought" may be used (col. 9, lines 53-60). The analysis of additional cancer cell-specific epitopes which will enable the cytopathologist to identify the origin of the cancer cells would be useful. Rimm teaches that "since the analysis of this invention is non-destructive of the cells, the cells may be removed from the sampling tube for additional analysis by other methods such as PCR (col. 12, lines 8-11)(limitations of Claim 41c).

Ts'o et al (herein referred to as Ts'o) teaches obtaining a sample comprising cancer cells and non-rare cells, subjecting the sample to multiple density gradient separation, subjecting the second fluid to a binding agent that binds non-rare cells and removes the bound non-rare cells from the fluid such that the fluid is enriched with a greater density of cancer cells (abstract). Ts'o teaches further processing the rare cells to detect expression of specific nucleic acids, chromosomal changes. FISH and combination staining are taught to provide improved methods of diagnosis, staging, and monitoring cancer in a patient (col. 2, lines 45-58). In a specific example, Ts'o teaches that in the case of separation of cancer cells from blood, it was found that cancer cells could be almost completely separated from nucleated white blood cells to provide the benefit of removing nucleated white blood cells which can interfere with cell identification, particularly wherein PCR methods are used (col. 11, lines 55-63). Ts'o teaches that rare cells can be also identified and or characterized using nucleic acid hybridization protocols.

Moreover, Hoon et al. (herein referred to as Hoon) teaches methods of using multiple cancer makers provide increased sensitivity over methods using single cancer markers. Hoon teaches the prior art was limited by their ability to discriminate cancer cells from normal cells also carrying the marker, thus reducing the specificity and reliability. Hoon teaches that "tumor, heterogeneity has caused sensitivity problems where a single-specific marker has been employed" (col. 2, lines 23-29). Hoon provides a list of makers which are preferably detected, including tyrosinase, MAGE3, Cytokeratin 20 (col. 3, lines 15-30). Hoon teaches that the method is conducted at

least twice on a given sample using at least two different primer pairs specific for two different specific markers (col. 4, lines 37-40). In a specific example, 15ml of blood was obtained from patients and collected in 5 sodium citrate tubes (col. 19, lines 22-23). The tubes were centrifuged and the buffy coat was removed. Analysis was performed on the blood specimens by PCR using multiple markers. The use of more than one marker can verify the presence of occult melanoma cells and significantly increase the sensitivity of detecting melanoma cells that express few or no copies of tyrosinase mRNA (col. 21, lines 60-65).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have combined the methods of Jung and Rimm because Hoon teaches that detection of multiple cancer makers provide increased sensitivity over methods using single cancer markers. Therefore, the ordinary artisan would have been motivated to have combined several cancer detection methods for several markers to increase sensitivity. The methods of Jung and Rimm both are directed to methods which allow detection of cancer-associated or cancer-specific markers within a body fluid, namely blood, which indicates an increased risk for or the presence of a disseminated cancer cell. The method of Jung detects amplification without the need for enrichment, whereas the method of Rimm isolates cancer cells and subsequently suggests performing additional analysis including PCR. The collection of two tubes of blood from a cancer patient or a patient suspected of having cancer and performing the analysis of both Jung and Rimm allows for the detection of multiple markers which increases sensitivity and increases the likelihood of early detection of cancer, as taught by Hoon.

Jung teaches numerous reasons why it is advantageous to use peripheral blood including that it is less stressful for the patient and therefore may be performed on a routine basis together with other laboratory tests. Therefore, when blood is drawn from a patient having cancer or suspected of having metastasis, several tubes may be collected with minimal discomfort or stress for the patient. The multiple tubes of blood may be used for a variety of laboratory tests including RT-PCR and cancer cell isolation. As specifically provided by Hoon, detection of more than a single cancer marker is strongly recommended to provide more sensitive and accurate results. Therefore, analyzing a single patient's blood samples for more than one known cancer marker would have the expected benefit of minimizing the stress and pain inflicted on the patient while simultaneously obtaining sensitive and meaningful results to determine whether micrometastasis is present in the sample. The same cancer-specific or cancer-associated marker may be detected in the enriched and unenriched sample in the event that no marker detection was seen in the unenriched sample, the ordinary artisan may be motivated to analyze an enriched sample in order to detect smaller quantities of the marker without background.

Response to Arguments

The response traverses the rejection. The response asserts that Jung, Rimm or T'so in view of Hoon do not teach or suggest all of the limitations of the claimed method. The response spends time discussing why each of the references individually fails to meet all the limitations of the claims. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references

individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The response, in discussing Rimm, argues that "Rimm et al. do not suggest the desirability of combining the method taught therein with any other method known in the art for detecting a first cancer related nucleic acid...." This argument has been reviewed but is not convincing because the Hoon has been used to demonstrate the desirability of combining methods for multiple marker detection. The response additionally argues that Rimm teaches away from the RT-PCR method by stating that RT-PCR is not a practical technique for detecting circulating cancer cells. This argument has been thoroughly reviewed, but is not found persuasive because the references teaches that RT-PCR requires that the origin of the tumor being sought be known in order to select for the specific molecular species. Rimm teaches that the techniques are not practical especially in point of care applications, by virtue of their cost and/or nature (col. 2, lines 20-38). Thus, taking the teachings of Rimm in totality, Rimm appears to state the when the source of the tumor is unknown, RT-PCR is less practical. This does not indicate that a method using RT-PCR is not obvious, but rather may suggest that additional assays will be required. Thus, the ordinary artisan would also be motivated to assay using the methods of Rimm and Jung (i.e. a RT-PCR assay) to obtain the benefits of each of the methods such that optimal results are obtained.

Moreover, in the discussion of Hoon, the response does not appear to fully acknowledge the teachings of Hoon. Hoon was used as motivation for combining

methods of detecting multiple markers to increased sensitivity. The response also argues that Hoon does not detect the presence of the same markers in cells from the same subject. The methods of Hoon appear to sample both lymph nodes and biopsies. The lymph nodes were found to be negative or normal in numerous individuals. Therefore, the cells were compared to normal tissues in the same subject.

The response argues that the action fails to point to any teaching, suggestion, or motivation for a person having ordinary skill in the art to modify or combine the cited documents to achieve the claimed invention with a reasonable expectation of success. In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the art clearly demonstrates that each of the assays within the claim are taught in the art. The response appears to be arguing that it is not suggested to combine two known methods to form a single method of detecting micrometastasized cells. Hoon clearly teaches that methods using multiple markers provide increased sensitivity over existing methods. While Hoon does not specifically teach using a method which requires isolation and a method which does not require isolation, the combination of known methods for detecting various markers is suggested. Unlike the response suggests, the teachings of

Rimm suggest that different makers are ideally assayed for using either isolation methods or lacking isolation methods. Therefore depending on the particular markers of choice by the practitioner, an assay require isolation and a method lacking isolation would be obvious. For example, when a patient with a particular cancer is assayed for BRAC1 or p53, for example, the method of choice (i.e. with isolation or lacking isolation) will be specific to the particular marker. Therefore, the suggestion in the art by Hoon that multiple markers provide increase sensitivity meets the required suggestion that the two methods may be combined into a single more sensitive assay. The instant specification fails to provide any reasons why the performance of the two separate well known methods to detect micrometastasized cells is unexpected. The ordinary artisan would have recognized, given the teachings of Hoon, that performance of two methods to detect two makers would provide increased sensitivity. Therefore, the performance of two known methods for detecting micrometastasis would have been an improvement over performing only one of the assays. Thus for the reasons above and those already of record, the rejection is maintained.

8. Claims 29-31, 33-35, 46-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jung et al. (Eur. J. Clinical Chemistry and Clinical Biochemistry. Vol. 35, No. 1, pages 3-10 January 1, 1997) and Rimm et al (US Pat. 6,197,523, March 2001) or Ts'o et al (US Pat 5,962,237, October 1999) in view of Hoon et al (US Pat 6,057,105, May 2, 2000) as applied to Claims 21-22, 24-28, 32, 36-37, 41-45, 49-51, 54-59 above and further in view of Schmitz et al. (US Pat. 6,190,870, February 20, 2001) in view of Popescu et al (Cancer Genetics Cytogent. Vol. 93, pg 10-21, 1997) or

Torczynski et al (US Pat. 5,589,579, December 1996) and in further view of Hoon et al (US Pat 6,057,105, May 2, 2000).

Neither Jung, Rimm, Ts'o or Hoon specifically teach the analysis of oncogenes, tumor suppressor genes, or other specifically recited genes.

However, Schmitz et al (herein referred to as Schmitz) teaches that tumor cells, particularly carcinoma cells are separated from peripheral blood by magnetic sorting (abstract). Specifically Schmitz teaches that cell samples may be contacted with antibodies which are directed to tumor antigens or lineage specific antigens are used to magnetically label the tumor cells. The labeled cells are separated from unlabeled hematopoietic cells by magnetic separation. The fraction of cell enriched for tumor cells is useful for quantitating the tumor cells and as a source of tumor cells for further characterization (col. 3, lines 30-45). Schmitz provides a long list of separation markers which may be cell surface antigens or located in the cytoplasm of the tumor cells. These markers include EMA, HEA-125, C26, among many others (col. 4). Moreover, Schmitz teaches that tumor cells may be further characterized as to their phenotype by PCR, FISH in situ FISH competitive hybridization (col. 9, lines 4-6). Moreover, the expression of a number of proteins related to malignancy is of interest including oncogenes, erbB, myc, p53, drug resistance proteins, metastatic factors including metalloproteases, integrins, angiogenic factors and others (col. 9, lines 8-15)(limitations of Claims 33-36).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Jung, Rimm, Ts'o

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in view of Hoon with the teaching of Schmitz that certain markers are of interest in cancer. Schmitz teaches numerous genes which are differentially expressed between cancer and normal cells, such that the ordinary artisan would be motivated to have selected any combination of such markers depending upon the suspected form of cancer in which they are studying or select a combination which is more general to cancers generically.

9. Claims 38-39, 52-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mitsuhashi (US Pat. 5,976,797) in view of Jung et al. (Eur. J. Clinical Chemistry and Clinical Biochemistry. Vol. 35, No. 1, pages 3-10 January 1, 1997) and Rimm et al (US Pat. 6,197,523, March 2001) or Ts'o et al (US Pat 5,962,237, October 1999) in view of Hoon et al (US Pat 6,057,105, May 2, 2000) as applied to Claims 21-22, 24-28, 32, 36-37, 41-45, 49-51, 54-59 above.

Neither Jung, Rimm, Ts'o nor Hoon teach analyzing and identifying an anticancer therapy by administering an anticancer therapy to samples, and detecting the presence or expression of markers before and after to evaluate an anticancer therapy.

However, Mitsuhashi teaches a method for determining the cytotoxic effect of a compound by adding said compound to a sample, measuring mRNA present in sample and evaluating the cytotoxic effect of the compound. Mitsuhashi teaches studying vinblastine, cisplatin and mitomycin C.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art to have modified the method of Mitsuhashi for detecting cytotoxic effects of a

anticancer compound such as cisplatin, for example, by detecting multiple markers in enriched and unenriched cultures. The ordinary artisan would have been motivated to have analyzed more than one mRNA for the reasons of specificity and reliability provided by Hoon. Determining the effect of an anticancer compound, or any compound, is accomplished by testing the nucleic acid expression prior to the administration of the compound, administering the compound and then comparing the expression following the compound administration. Therefore, the claimed methods are not novel with respect to the means in which an anticancer therapy is analyzed.

Response to Arguments

The response traverses the rejection. The response asserts that Jung, Rimm, Ts'o and Hoon fail to teach the method. This argument has been reviewed but is not convincing for the reasons presented above.

The response further argues that there is no motivation to combine. This argument has been thoroughly reviewed, but is not found persuasive because the art clearly teaches that anticancer compound effects are analyzed by determining the effect in treated and non-treated samples. Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

10. No claims allowable over the art.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP

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§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).


A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.


Jeanine Goldberg
May 30, 2003


GARY BENZION, PH.D.
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600